II. REMARKS

Claims 1-29 are pending stand rejected under 35 U.S.C. §§ 112, first and second paragraphs, 102 and 103. Applicant notes with appreciation that the restriction requirement has been withdrawn.

Claim 1 has been amended to specify that the immunogenic composition comprises a DNA immunogen and BLC or a polynucleotide encoding BLC. Support for the amendment can be found throughout the application as filed, for example in original claim 9. Claims 8 and 9 have been canceled without prejudice or disclaimer. Claim 11 has been amended to specify that the administering is intradermal or intramuscular and that the DNA immunogen is a viral immunogen. Support for the amendments to claim 11 can be found throughout the application as filed, for example on page 8, line 6 and page 5, line 17. The amendments to claims 1 and 11 are made to solely to expedite prosecution and are in no way intended as an acknowledgment as to the correctness of the Examiner's position. Finally, claim 25 has been amended herein to correct a typographical error relating to dependencies. Applicant reserves the right to file a continuation application directed to the subject matter of the original claims at any time during the pendency of this application. No new matter has been added as a result of these amendments and entry thereof is respectfully requested.

In view of the foregoing amendments and following remarks, Applicant respectfully requests reconsideration of the restriction requirement and of the application.

35 U.S.C. § 112, First Paragraph, Enablement

Claims 1, 9, 11 and 22 stand rejected under 35 U.S.C. 112, first paragraph as allegedly not enabled by the specification as filed. (Office Action, page 4). It is acknowledged that the specification enables enhancing an antibody-based response to HIV gag by intramuscular or intradermal injection of nucleic acids encoding HIV gag and B lymphocyte chemokine. (Office Action, page 2). Nonetheless, it is alleged that the specification does not reasonably enabled enhancing a cytotoxic T lymphocyte response

to any antigen and by any means of administration and that it would require undue experimentation to practice the invention of claims 1, 9, 11 and 22. In sum, the current rejection is based on the assertion that "the specification fails to teach whether chemokines would increase antibody responses to other antigens, particularly antigens that do not usually cause an antibody response, whether it could enhance a cellular immune response and fails to teach whether any route of administration could enhance such responses." (Office Action, page 3).

Applicant traverses each and every basis of this rejection and address them in turn.

Applicant again notes that the test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. *Ex parte Forman*, 230 USPQ 546 (BPAI 1986). When determining whether the amount of testing required is "undue," the courts have determined that "time and difficulty of experiments are not determinative if they are merely routine." (see, *e.g., In re Wands,* 8 USPQ2d at 1404, citing *In re Angstadt*, 190 USPQ 214 (CCPA 1976). In the pending case, pending claims 1, 11 and 22 are fully enabled by the specification as filed throughout their scope.

The Specification as Filed Enables Claims 1, 9, 11 and 22 Throughout Their Scope

The Office has acknowledged that the specification enables a skilled artisan to practice the claimed invention using HCV immunogens and a polynucleotide encoding MIP-1α in baboons. (See, Paper #7, page 4). In addition, it is now acknowledged that the specification enables enhancing an antibody-based response to HIV gag by intramuscular or intradermal injection of nucleic acids encoding HIV gag and B lymphocyte chemokine (BLC). (See, Office Action, page 2). Nonetheless, it is asserted that the specification does not provide sufficient guidance as to enhancing antibody responses to antigens other than HIV gag, particularly "antigens that do not usually cause an antibody response." (Office Action, page 3).

In this regard, Applicant notes that there is no legal obligation to specifically recite (or exemplify) each and every DNA immunogen that can be used in the compositions and methods of claims 1, 11 and 22 (the subject matter of claim 9 has been incorporated into claim 1). In fact, as is well known to those of skill in the art, HIV gag is an excellent example of an antigen that does not, by itself, usually generate strong antibody responses. Indeed, HIV env is the preferred antigen for generating antibody responses. (See, *e.g.*, Hurwitz, discussed below). Thus, although Applicant is under no obligation exemplify enhancement of antibody responses to multiple antigens, actual working examples have been provided specifically relating to antigens that do not usually generate strong antibody responses. Simply put, the specification clearly satisfies the requirement with regard to antigens whose immunogenicity is enhanced by co-administration with a chemokine.

Finally, with regard to routes of administration, Applicant again notes that the methods can be practiced with any mode of administration. Solely to advance prosecution, claim 11 has been amended to specify the administration is intradermal or intramuscular. Accordingly, this rejection has been obviated.

In sum, despite the Office's failure to establish a *prima facie* case of non-enablement, Applicant has established that the specification fully enables the pending claims by enabling not only a single use, but by enabling pending claims 1, 11 and 22 throughout their scope.

The Cited References Do Not Establish Unpredictability

Applicant also traverses the Examiner's assertion that certain references establish that the claimed invention is unpredictable. (Gunn, McCluskie, and Nakano cited on pages 3-4 of the Office Action).

None of these references in any way establish unpredictability of the invention of pending claims 1, 11 and 22. Indeed, Gunn's teachings regarding BLC's and migration of T-cells is not relevant to the pending claims. Applicant's disclosure clearly

indicates that chemokines (such as BLC) act as attractants for one or more very specific molecules. (See, *e.g.*, page 4, lines 3-12). At the same time, Applicant's disclosure is clear that the attractant characteristics of a particular chemokine is not necessarily correlated with the claimed compositions or methods of enhancing immune responses. In other words, Applicant has demonstrated that chemokines can enhance immune responses regardless of what molecules they are known to attract. Thus, contrary to the Examiner's assertion, the specification does indeed teach that chemokines such as BLC and MIP can be used to enhanced immunogenicity.

With regard to McCluskie and Nakano, Applicant notes that the amendment to claim 11 has obviated any relevance these references may have to the subject matter of claims 1, 9, 11, and 22.

Thus, the cited references do not establish that methods of eliciting immune responses are not enabled by Applicant's specification. In fact, Applicant's specification describes and demonstrates the generation of an immune response and, accordingly, the various references cited by the Office are not relevant to the claimed invention and certainly do not establish unpredictability of the claimed invention.

For the all the foregoing reasons, Applicant submits that the specification fully enables the claims and respectfully requests withdrawal of this rejection.

35 U.S.C. § 112, Second Paragraph

The Examiner has rejected claims 23-26 under 35 U.S.C. §112, second paragraph, asserting that the claims are indefinite because of the improper dependency of claim 25. Applicant thanks the Examiner for bringing this typographical error to his attention and has amended claim 25 appropriately herein. Accordingly, this rejection has been obviated.

35 U.S.C. § 102 (e)

Claims 1, 8, 10-13, 16, 17, 21, 27 and 28 stand rejected under 35 U.S.C. § 102(e) as allegedly anticipated by U.S. Patent No. 6,383,774 (hereinafter "Chandrashekar"). Claims 1, 2, 5, 8, 10-13, 16, 17, 21, 25 and 27-29 stand rejected as allegedly anticipated by U.S. Patent No. 5,846,546 (hereinafter "Hurwitz"). Claims 1-8, 10-13, 16, 17, 21, 23-29 stand rejected as allegedly anticipated by U.S. Patent No. 6,355,247 (hereinafter "Selby"). Chandrashekar is cited for allegedly teaching immunogenic compositions comprising parasitic immunogens and antibody responses using these immunogens in combination with MIP-1α. (Office Action, page 6). Hurwitz is cited for allegedly disclosing an immunogenic composition comprising a DNA immunogen and MIP-1α and a method comprising administering to a mammal a chemokine and a DNA immunogen. (Office Action, page 7). Selby is cited for allegedly disclosing an immunogenic composition comprising a DNA immunogen and MIP-1α and a method comprising administering to a mammal a chemokine and a DNA immunogen. (Office Action, page 8).

Applicant traverses the rejections and supporting remarks.

It is axiomatic that in order to be an anticipatory reference, the single reference cited by the Office must disclose each and every element of the claims. *Hybritech v. Monoclonal Antibodies,* 231 USPQ 81 (Fed. Cir. 1986). Moreover, the single source must disclose all of the claimed elements arranged as in the claims. *See, e.g., Richardson v. Suzuki Motor Co.,* 9 USPQ2d 1913 (Fed. Cir. 1989). There must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention. *Scripps Clinic & Research Foundation v. Genentech, Inc.,* 18 USPQ2d 1896 (Fed. Cir. 1991).

Applying these rules to the case at hand, Applicant notes that pending composition claims 1-10 are clearly not anticipated by any of the cited references as none

of the cited references describe, demonstrate or suggest immunogenic compositions comprising a DNA immunogen and a BLC or a polynucleotide encoding a BLC.

With regard to method claims 11-29, Applicant submits, as a threshold matter, that Chandrashekar is not relevant to the pending clams as this reference fails to teach or suggest methods involving a viral DNA immunogen. Turning to Hurwitz and Selby, neither disclosure is identical to that of pending claims 11-29. Hurwitz plainly teaches that, when present, MIP is included for its antiviral chemotherapeutic effects. (See, Hurwitz, col. 29, lines 14-35). This is a far cry from suggesting or disclosing that chemokines enhance the immune response to a DNA immunogen. For its part, Selby fails to describe, demonstrate or suggest induction of an antibody responses at all. Rather, this reference is directed entirely to the induction of cell-mediated immunological responses. (See, column 2, lines 43 to 56). Further, both Hurwitz and Selby fail to provide any information actually disclosing that chemokines enhance the immune response to a viral DNA immunogen. Accordingly, as there is not identity between the methods of claims 11-29 and the disclosures of Hurwitz and Selby, anticipation has not been established and withdrawal of this rejection is respectfully requested.

35 U.S.C. § 103

Claims 1-8, 10-21 and 23-29 stand rejected as allegedly obvious over Hurwitz and Selby and in further view of U.S. Patent No. 6,214,540 (hereinafter "DeVico"). Hurwitz and Selby are cited as above. DeVico is cited for teaching the use of chemokines for HIV therapy using chemokines. Thus, the Office Action states:

> ...it would have been obvious to one or ordinary skill in the art at the time the invention was made to modify the methods taught by Hurwitz et al, Selby et al, and DeVico et al. by administering the immunogen and chemokine together or separate with a reasonable expectation of success because ever chemokine alone could achieve a therapeutic effect. The ordinary skilled artisan would have been motivated to modify the method for enhanced immune response against virus and tumor. Thus, the claimed invention as a whole was clearly *prima facie* obvious in the absence of evidence to the contrary. (Office Action, page 9).

Applicant traverses the rejection and supporting remarks.

The Examiner bears the burden of establishing a *prima facie* case of obviousness. *See, e.g., In re Ryckaert,* 28 USPQ2d 1955, 1956 (Fed. Cir. 1993); and *In re Oetiker,* 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). The reference must teach all the limitations of the claimed invention and, moreover, suggests the desirability of arriving at the claimed subject matter. (*See, e.g., Amgen, Inc. v. Chugai Pharm. Co.,* 18 USPQ2d 1016, 1023 (Fed. Cir. 1991) stating that "hindsight is not a justifiable basis on which to find that the ultimate achievement of along sought and difficult scientific goal was obvious" and *In re Laskowski,* 10 USPQ2d 1397, 1399 (Fed. Cir. 1989) stating that "the mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability of the modification.") Thus, even if individual elements of the invention are taught in the prior art, such is not, in and of itself, sufficient to make out a case of *prima facie* obviousness. See, *Symbol Technologies, Inc. v. Opticon, Inc.*, 19 USPQ2d 1241 (Fed. Cir. 1991) ("We do not pick and chose among the individual elements of assorted prior art references to deprecate the claimed invention, but rather, we look for some teaching or suggestion in the references to support their use in the particular claimed combination.").

Moreover, that which is "inherent" in a reference, if not known at the time of the invention, cannot form the basis for rejecting the claimed invention as obvious under section 103. *See, e.g., In re Shetty*, 195 USPQ 753 (CCPA 1977). Thus,

> "The inherency of an advantage and its obviousness are entirely different questions. That which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown." *In re Shetty, supra* quoting *In re Sporman,* 150 USPQ 449 (CCPA 1966).

Applying these rules to the pending case, Applicant submits that the Office has not established that the combination of references teaches all the limitations of the pending claims and, in addition, has not established that the references suggest the

desirability of the claimed invention. Moreover, the Office has improperly relied on information not known at the time of invention in making this rejection.

None of the references describe or demonstrate enhancing the immune response to a DNA immunogen using a chemokine (or a polynucleotide encoding a chemokine). Nowhere do Hurwitz, Selby or DeVico actually describe methods as claimed by Applicant. As noted above, Hurwitz refers to chemokines solely as antiviral chemotherapeutic compounds and, as such, does not teach or suggest methods for enhancing the immune response to a DNA immunogen using a chemokine as claimed. (See, Hurwitz, col. 29, lines 14-35). Similarly, DeVico is directed to the use of chemokines themselves as therapeutics for HIV. (See, DeVico, abstract and claims). The Examiner has not pointed to any suggestion in Hurwitz or DeVico that chemokines could act to enhance the immune response to a DNA immunogen.

For its part, Selby also fails to describe methods in which the immune response to a DNA immunogen is actually enhanced using a chemokine. None of Selby's examples include a chemokine (or polynucleotide encoding a chemokine) and its' effect on enhancing the immune response to the DNA immunogen. At best, Selby provides an invitation to experiment by indicating that MIP-1β may be involved in efficient antigen presentation or attraction of lymphocytes. (See, Selby, col. 8, lines 35-41). It is impermissible to base an obviousness rejection on an invitation to experiment or on something that was unknown at the time Selby was filed, namely that a chemokine (or polynucleotide encoding a chemokine) could enhance the immune response to a DNA immunogen.

Therefore, Applicant submits that the Examiner has failed to make out a *prima facie* case of obviousness because the references fail to teach or suggest each and every element of the invention recited in claims 11-29. There is simply no motivation within the references to arrive at the claimed invention.

III. CONCLUSION

For the reasons state above, Applicant respectfully submits that the pending claims define an invention which is novel and fully enabled by the specification. Accordingly, Applicant requests that the rejection of the claims be withdrawn, and that the application proceed to allowance.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§ 1.16 and 1.17 which may be required by this paper, or to credit any overpayment, to Deposit Account No. 18-1648.

Please direct all further communications regarding this application to:

Anne S. Dollard, Esq.
CHIRON CORPORATION
Intellectual Property - R440
P.O. Box 8097
Emeryville, CA 94662-8097

Respectfully submitted,

Date: August 19, 2002

By: D Pasternak
Dahna S. Pasternak
Registration No. 41,411

CHIRON CORPORATION
Intellectual Property - R440
P.O. Box 8097
Emeryville, CA 94662-8097
Telephone: (510) 923-2719
Facsimile: (510) 655-3542

Version Showing Changes Made to Claims

1. (Amended) An immunogenic composition comprising:
a DNA immunogen; and
a [chemokine] B lymphocyte chemokine (BLC) or a polynucleotide encoding a [chemokine] B lymphocyte chemokine (BLC).

11. (Amended) A method of enhancing an immune response to a DNA immunogen in a mammal comprising the step of:
intramuscularly or intradermally administering to the mammal (i) a chemokine or a first polynucleotide encoding a chemokine and (ii) a viral DNA immunogen, whereby an immune response to the DNA immunogen is enhanced.

25. (Amended) The method of claim [23] 11 wherein the polynucleotide encodes an HIV polypeptide.

Currently Pending Claims

1. (Amended) An immunogenic composition comprising:
a DNA immunogen; and
a B lymphocyte chemokine (BLC) or a polynucleotide encoding a B lymphocyte chemokine (BLC).

2. The immunogenic composition of claim 1 wherein the DNA immunogen comprises a polynucleotide encoding a viral immunogen.

3. The immunogenic composition of claim 2 wherein the polynucleotide encodes a hepatitis C virus non-structural polypeptide.

4. The immunogenic composition of claim 3 wherein the hepatitis C virus non-structural polypeptide is selected from the group consisting of NS3, NS4, NS5a, and NS5b.

5. The immunogenic composition of claim 2 wherein the polynucleotide encodes an HIV polypeptide.

6. The immunogenic composition of claim 5 wherein the HIV polypeptide is a gag polypeptide.

7. The immunogenic composition of claim 1 wherein the DNA immunogen comprises a polynucleotide encoding an immunogen expressed by a tumor.

8 and 9. Canceled.

10. The immunogenic composition of claim 1 further comprising a pharmaceutically acceptable carrier.

11. (Amended) A method of enhancing an immune response to a DNA immunogen in a mammal comprising the step of:
intramuscularly or intradermally administering to the mammal (i) a chemokine or a first polynucleotide encoding a chemokine and (ii) a viral DNA immunogen, whereby an immune response to the DNA immunogen is enhanced.

12. The method of claim 11 wherein a chemokine is administered.

13. The method of claim 12 wherein the chemokine and the DNA immunogen are co-administered.

14. The method of claim 12 wherein the chemokine is administered prior to the administration of the DNA immunogen.

15. The method of claim 12 wherein the DNA immunogen is administered prior to administration of the chemokine.

16. The method of claim 11 wherein the first polynucleotide encoding the chemokine is administered.

17. The method of claim 16 wherein the first polynucleotide and the DNA immunogen are co-administered.

18. The method of claim 16 wherein the polynucleotide is administered prior to the administration of the DNA immunogen.

19. The method of claim 16 wherein the DNA immunogen is administered prior tot he administration of the first polynucleotide.

20. The method of claim 16 wherein a second polynucleotide which comprises (a) the first polynucleotide and (b) the DNA immunogen is administered.

21. The method of claim 11 wherein the chemokine is macrophage inflammatory protein 1α (MIP-1α).

22. The method of claim 11 wherein a chemokine is B lymphocyte chemokine (BLC).

23. The method of claim 11 wherein the DNA immunogen comprises a polynucleotide encodes a hepatitis C virus non-structural polypeptide.

24. The method of claim 23 wherein the hepatitis C virus non-structural polypeptide is selected from the group consisting of NS3, NS4, NS5a, and NS5b.

25. (Amended) The method of claim 11 wherein the polynucleotide encodes an HIV polypeptide.

26. The method of claim 25 wherein the HIV polypeptide is a gag polypeptide.

27. The method of claim 11 wherein the mammal is human.

28. The method of claim 11 wherein the immune response is an antibody response.

29. The method of claim 11 wherein the immune response is a cytotoxic T lymphocyte response.